

Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1-14, 22-40, 47-93, and 97 are pending in the application, with 1, 47, 48, 51, 57, 64, 66, 73, 76, and 83 being the independent claims. Claims 94-96 are sought to be cancelled without prejudice to or disclaimer of the subject matter therein. Support for the amendments are found in the claims as originally filed and in the specification at page 33, lines 1-22. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Election/Restriction

Claims 1-5, 35, 49, 51, 54-59, 62, 64, 66-68, 75-78, and 85-97 have been rejected as being drawn to an improper Markush grouping. The Examiner is of the opinion that “[a] reference anticipating one invention, would not render obvious the others, for example a thiazepine ring is different from thiazocene, thiazine, thiazolidine, etc.” (Office Action, page 3).

Applicants respectfully disagree. Independent claims 1, 51, 57, 66, and 76 as amended refer only to compounds wherein A² is a monocyclic ring selected from

heteroarylene or unsaturated, partially unsaturated, or saturated heterocycloalkylene containing a total of 7 ring atoms. Therefore, Applicants respectfully submit that the Examiner's stated grounds for rejection have been accommodated and the rejection should be withdrawn.

Rejections under 35 U.S.C. § 112

A. *First Rejection (Claims 1-14, 22-40, and 47-97)*

Claims 1-14, 22-40, and 47-97 have been rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which allegedly was not described in the specification in such a way as to enable one skilled in the art to use the invention. (Office Action, pages 3-4). Applicants respectfully traverse this rejection.

Claim 96 has been canceled rendering this aspect of the rejection moot.

The Examiner is of the opinion that:

[t]he term prodrug is of indeterminate scope in that they vary widely from drug to drug. It is not known which moiety of formula (I) would form the basis for the prodrug. Every ester, amide and carbamate in theory is biohydrolyzable, i.e. is capable in some degree of hydrolyses. Not to mention the many in vivo environments that this occurs in. . . . The nature of the invention in the instant case, has claims which embrace substituted thiazepine compounds. The instant compounds of formula (I) wherein the prodrugs are not described in the disclosure in such a way [that] one of ordinary skill in the art would [know] how to prepare the various compounds suggested by claims 1-14, 22-40 and 47-97. In view of the lack of direction provided in the specification regarding starting materials, the lack of working examples, and the general unpredictability of chemical reactions, it would take an undue amount of experimentation for one skilled in the art

to make the claimed compounds and therefore practice the invention.

(Office Action, page 4).

Applicants respectfully disagree. The structures of "prodrugs" for the compounds of the invention are defined in the specification at page 33, lines 1-22.

The word "prodrug" is a term of art, well known to one of ordinary skill in the art. The specification provides a definition of prodrugs, provides a list of exemplary compounds that can be used to form prodrugs and provides references discussing the structure and use of prodrugs. Thus, Applicants' use of the word prodrug accords with the word's ordinary meaning and the term is sufficiently described in the specification to enable one of skill in the art to practice the claimed invention. However, in the interest of advancing prosecution, independent claims 1, 47, 48, 51, 57, 64, 66, 73, 76, and 83 have been amended to recite that a prodrug derivative is an ester of a compound comprising a hydroxy or carboxy group. The specification discloses examples of suitable esters and provides references discussing such esters (page 33, lines 1-22). Therefore, Applicants respectfully submit that the Examiner's stated grounds for rejection have been accommodated and the rejection should be withdrawn.

B. Second Rejection (Claims 54-56 and 66-88)

Claims 54-56 and 66-88 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. (Office Action, pages 5-6). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that:

[i]n the art of clinical oncology, no compound has yet shown clinical efficacy against every type of cancer. To quote Salmon (Principles of Cancer Therapy) in the paragraph on page 1038 titled Medical Therapy "Curative therapy has been developed for a series of relatively uncommon neoplasms and useful palliative therapy has been developed for some common forms of cancer (Table 162-4). With rare exceptions, effective therapy has utilized combinations of anticancer drugs." Applicant's attention is drawn to Tables 162-6, 162-7, 162-8, 162-162-9 [sic], 162-10, and the material on pages 1045-1046 titled Miscellaneous Anticancer Agents in Salmon (Principles of Cancer Therapy). Different agents are used for different specific forms of cancer and no single agent is listed as a treatment of every single type of cancer. To quote Balasubramanian (Recent Developments in Cancer Cytotoxics) from page 151 first paragraph "[t]he successful treatment of solid tumors remains a formidable challenge. The partial success of traditional cancer chemotherapy...". On page 158, second paragraph Balasubramanian (Recent Developments in Cancer Cytotoxics) states: "The future scenario in clinical management of cancer will be mainly dictated by the availability of less toxic and tumor selective agents". No compound has shown clinical efficacy against all cancers, thus no *in vivo* or *in vitro* assay could be validated for the identification of such a general agent. Applicants' specification logically must lack such assay data.

To make clearer the lack of enablement for treatment of all cancer, extrinsic evidence is supplied by Draetta (Ann. Reports Med. Chem.), final sentence on page 246 "Although many still think about the need for a magic bullet as a cure for all cancers, our knowledge of the molecular mechanism underlying this disease make the prospect of developing such a universal cure very unlikely." Since no universal cure for cancer has been developed, it follows that there is no correlation between the assays relied upon by applicants and the ability to treat all cancers. Thus, those assays are not sufficient to enable such claims.

(Office Action, pages 5-6). Applicants respectfully disagree with the Examiner's analysis and conclusions.

The Examiner cites several references to support her contention that no single anticancer compound can effectively treat all cancers. However, the enablement of the present claims does not require the existence of such a "magic bullet." In order for the present claims to be enabled for the treatment of cancer, it is sufficient that the class of compounds as a whole described in the claims has caspase activating activity and that administration of compounds having such activity is capable of treating cancers in general. To the extent that any particular compound within the genus is not effective or that any particular type of cancer does not respond to the administration, these are merely inoperative embodiments of the claimed invention. As long as the skilled artisan can readily determine which embodiments are inoperative without undue experimentation, the invention as a whole is enabled. See M.P.E.P. 2164.08(b). The examples disclosed in the present specification involving three types of cancer cells and five different compounds of the claimed invention indicate that the compounds are effective in inducing apoptosis in cancer cells. The Examiner has provided no specific evidence to show that this activity is not common to all the compounds encompassed by the invention, that the disclosed examples are not predictive of effective treatment of cancer *in vivo*, or that any cancer would not be sensitive to the induction of apoptosis. The Examiner argues that since there are no magic bullets, no assay can be validated for the identification of a magic bullet, so the assay data in the present specification can be ignored. This is an improper analysis. As discussed above, the enablement of the present claims does not depend on the identification of a single compound capable of curing all cancers. The assays disclosed in the specification are predictive of *in vivo* efficacy and the Examiner has failed to provide any evidence to the

contrary. In the absence of any such specific evidence showing that the specification is not enabling for the claimed invention, the invention must be considered to be enabled.

Additionally, Applicants provided evidence of the broad applicability of the present invention in the response filed February 5, 2003. The Examiner has failed to address this evidence. It is now known that cancer cells are, *inter alia*, generally characterized not only by a loss of cell cycle control but also by resistance to apoptosis. *See generally* Raymond W. Ruddon, *Biochemistry of Cancer*, in *Holand-Frei Cancer Medicine*, Chapter 2 (Robert C. Blast, Jr., *et al.* eds., 5th ed., B.C. Decker, 2000), a copy of which was submitted as Document AT19 in the First Supplemental Information Disclosure Statement filed February 5, 2003. Consequently, increasing the rate of apoptosis is recognized by those of skill in the art as an effective method for the treatment of a wide variety of cancers. *See, e.g.*, WO 00/04901, page 3, line 3, through page 5, line 6, a copy of which was submitted as Document AL2 in the First Supplemental Information Disclosure Statement filed February 5, 2003. Indeed, caspase activation is recognized, by those of skill in the art of cancer therapy, as a crucial requirement for the sensitivity of tumor cells toward drug-induced cell death. *See, e.g.*, Maret Los, *et al.*, "Cross-Resistance of CD95- and Drug-Induced Apoptosis as a Consequence of Deficient Activation of Caspases (ICE/Ced-3 Proteases)," *Blood* 90:3118-3129, 3128 (1997), a copy of which is submitted as Document AT9 in the Information Disclosure Statement filed November 4, 2002. Therefore, it is now recognized by those of skill in the art that agents that increase the rate of apoptosis are effective for the treatment of a wide variety of cancers.

For the reasons stated above, Applicants respectfully submit that the evidence submitted herewith is effective to rebut a *prima facie* case for non-enablement of claims 54-

56 and 66-88, under 35 U.S.C. § 112, first paragraph, and that the rejection should be withdrawn.

C. Third Rejection (Claims 57-65, 89-93, 96 and 97)

Claims 57-65, 89-93, 96 and 97 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. (Office Action, pages 6-7). Applicants respectfully traverse this rejection.

Claim 96 has been canceled rendering this aspect of the rejection moot.

The Examiner is of the opinion that:

[t]here is no basis for the treatment of the asserted diseases and/or disorders in the specification, nor is there any testing to indicate that the compounds of the instant invention are effective in the treatment of the asserted disease and/or disorders.

(Office action, page 7).

Applicants respectfully disagree. It is well known to those of skill in the art what disorders are responsive to the induction of apoptosis. See, e.g., O'Reilly, *et al. Inflamm. Res.*, 48:5-21 (1999), submitted as document AS11 in the Information Disclosure Statement filed November 4, 2002. O'Reilly states "[a]poptosis has been recognized as an important regulator of tissue development and cellular homeostasis and abnormalities in this process have been implicated as a cause or contributing factor in a broad range of human diseases, including autoimmunity." O'Reilly at 14. See, also, Orrenius, *J. Intern. Med.*, 237:529-536 (1995), submitted as document AR12 in the Information Disclosure Statement filed

November 4, 2002. Orrenius states "[f]inally, it has also become increasingly clear that apoptosis plays an important role in a number of diseases, including autoimmune disease, neurodegenerative disease, cancer and HIV/AIDS." Orrenius at 532. Thus, one of skill in the art would be apprized of what diseases or disorders to treat using the present invention based on the level of knowledge in the art and the teachings of the invention.

Further, examples of particular diseases and its symptoms the invention is used to treat can be found in the specification, *inter alia*, at page 35, line 15, through page 36 line 5. Additional diseases are disclosed in the specification at page 38, line 24 through page 41, line 30. Furthermore, methods of treatment are described, *inter alia*, at page 36, line 6 through page 38, line 9 and at page 42, line 1, through page 46, line 10. Finally, the specification describes the animals intended to be treated with the invention on page 27, lines 13-15.

The Examiner indicates that there is no basis for the treatment of the asserted diseases or disorders but provides no reasoning whatsoever to support this conclusion. The Examiner further states that no testing has been done to prove the effectiveness of the treatment. However, there is no requirement for working examples in order for a claim to be enabled. See M.P.E.P. 2164.02.

Therefore, Applicants respectfully submit the Examiner has not established a *prima facie* case of non-enablement of claims 57-65, 89-93, and 97 under 35 U.S.C. § 112, first paragraph; and Applicants respectfully request that the rejection be withdrawn.

D. Fourth Rejection (Claims 1-14, 22-40, and 47-97)

Claims 1-14, 22-40, and 47-97 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite (Office Action, pages 7-8). Applicants respectfully traverse this rejection.

Claims 94-96 have been canceled rendering this aspect of the rejection moot.

The Examiner is of the opinion that:

[d]erivatives includes more than is positively recited. With respect to derivatives, the applicant's specification does not sufficiently define the applicants metes and bounds of the compounds as claimed herein. It is recognized that a protecting group is often used in a process, however, it is the compounds which are being claimed and "protected derivatives" does not defined the compounds which the applicants are seeking patent protection for.

(Office Action, pages 7-8).

Applicants respectfully disagree. The specification clearly defines what is meant by the terms N-oxide derivatives and protected derivatives. The term N-oxide derivative is defined at page 31, lines 26-28, where it is stated that it is a derivative of a compound of Formula I in which nitrogens are in an oxidized state (*i.e.*, O-N) and which possess the desired pharmacological activity. It is clear what is encompassed by this definition as it only encompasses compounds of Formula I in which the nitrogens are oxidized. The treatment of nitrogen-containing compounds with an oxidizing agent to form N-oxides is a standard reaction for those of skill in the art of organic chemistry. The Examiner has not provided any indication of derivatives other than what is positively recited which fall under the

definition provided in the specification. The Examiner has not provided any reason why one of skill in the art would fail to recognize the metes and bounds of the claims.

Similarly, the term protected derivative is clearly defined in the specification at page 33, lines 23-29, where it is stated that it is a derivative of compounds of the invention in which a reactive site or sites are blocked with protecting groups. It is clear what is encompassed by this definition as it only encompasses claimed compounds in which one or more reactive sites are blocked with protecting groups. The specification further provides reference to a comprehensive list of protecting groups that are routinely used in organic chemistry. Thus, the term derivative as used here is clearly defined by the specification. The Examiner acknowledges that protecting groups are often used, and fails to provide any reason why one of skill in the art would fail to recognize the metes and bounds of the claims.

The Examiner is of the opinion that the claims are indefinite "in that it is not known which diseases are capable of being responsive to the induction of apoptosis. The scope of diseases and/or disorders associated with the induction of apoptosis could alter over time. The applicants' are not entitled to preempt the efforts of others."

Applicants respectfully disagree. As discussed above, disorders responsive to the induction of apoptosis are well known in the art. Thus, one of skill in the art would be apprized of what diseases or disorders to treat using the present invention based on the level of knowledge in the art and the teachings of the invention.

Further, a long list of diseases and their symptoms the invention may be used to treat can be found in the specification, *inter alia*, at page 35, line 15, through page 36 line 5. Additional diseases are disclosed in the specification at page 38, line 24 through page 41, line 30. Furthermore, methods of treatment are described, *inter alia*, at page 36, line 6

through page 38, line 9 and at page 42, line 1, through page 46, line 10. Finally, the specification describes the animals intended to be treated with the invention on page 27, lines 13-15.

Applicants have discovered compounds that are useful for the treatment of diseases/disorders responsive to the induction of apoptosis. Applicants therefore deserve protection for the treatment of any disease/disorder falling into this category with the disclosed compounds. The possibility of discovery of new diseases that are also responsive to the induction of apoptosis should not limit Applicants' invention, which is broadly applicable.

It is noted that claim 97 lists specific diseases that are responsive to the induction of apoptosis. Thus, the present rejection should not apply to claim 97.

Therefore, Applicants respectfully submit the Examiner has not established a *prima facie* case of indefiniteness under 35 U.S.C. § 112, second paragraph; and Applicants respectfully request that the rejection be withdrawn.

E. *Fifth Rejection (Claim 97)*

Claim 97 has been rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession if the claimed invention. (Office Action, page 9). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that the "addition of claim 97, which includes a list of disorders, some which are not described in the specification, i.e. rheumatoid arthritis, autoimmune lymphoproliferative syndrome, etc. Applicant is required to cancel the new matter in the reply to this Office action." (Office action, page 9).

Applicants respectfully disagree. Each of the disorders listed in claim 97 finds support in the present specification. In particular, rheumatoid arthritis is disclosed at page 41, lines 3-15 and autoimmune lymphoproliferative syndrome is disclosed at page 39, lines 6-11. Therefore, Applicants respectfully submit that the Examiner's stated grounds for rejection have been addressed and the rejection should be withdrawn.

F. *Sixth Rejection (Claims 1-5, 8, 22, 24, 26, 35, 48, 49, 51-64, 66-72, 75-83, and 85-97)*

Claims 1-5, 8, 22, 24, 26, 35, 48, 49, 51-64, 66-72, 75-83, and 85-97 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite (Office Action, page 10). Applicants respectfully traverse this rejection.

Claims 94-96 have been canceled rendering this aspect of the rejection moot.

The Examiner is of the opinion that claims 1-5, 22, 24, 26, 35, 49, 51, 54-59, 66-68, 75-78, and 87-97 "are vague and indefinite in that it is not known what is meant by the definition of R¹, where R¹ is as defined below. There is no definition of R¹ below."

Applicants respectfully disagree. Independent claims 1, 51, 57, 66, and 76 as amended do not refer to the definition of R¹ below. Thus, the claims are not indefinite.

The Examiner is of the opinion that claims 1-5, 35, 49, 51, 54-59, 62, 64, 66-68, 75-78, and 87-97 are indefinite as there is insufficient antecedent basis for the limitation "A²is a fused polycyclic ring system" in the proviso.

Applicants respectfully disagree. Claims 1, 49, 51, 57, 66, and 76 as amended do not contain the proviso. Thus, the claims are not indefinite.

The Examiner is of the opinion that claims 8, 63, 72, and 82 are indefinite as there is insufficient antecedent basis for the limitation "bis-trifluoromethyl phenyl."

Applicants respectfully disagree. Claim 8 is dependent from claim 1, in which the definition of A³ indicates that each ring within A³ that contains from 3 to 8 ring atoms may be substituted with 1 to 3 groups independently selected from a group of substituents including halo-substituted (C₁₋₆)alkyl. Similarly, claims 63, 72, and 82 are dependent from claims 57, 66, and 76, which contain the same definition of A³ as in claim 1. Thus, there is sufficient antecedent basis for the term "bis-trifluoromethyl-phenyl."

The Examiner is of the opinion that claim 48 is "vague and indefinite in that it is not known what is meant by the definition of A², where A² is defined as above. There is no definition of A² above."

Applicants respectfully disagree. Claim 48 does not contain the specified wording regarding A². Thus, the claim is not indefinite. If the Examiner intended the rejection to be directed to claim 49, claim 49 as amended indicates that A² is as defined in Claim 1. Thus, the claim is not indefinite.

The Examiner is of the opinion that claims 51-53 are indefinite as "it is not known what is meant by the definition of A² is -R⁸. It is believed that the applicants' intended X²R⁸."

Applicants respectfully disagree. Claim 51 as amended recites in part "A² may be substituted with a group selected from X²R⁸." Thus, the claims are not indefinite.

The Examiner is of the opinion that claims 51-53 are indefinite as "it is not known what is meant by the definition of A³ is -R⁹. It is believed that the applicants' intended X²R⁹."

Applicants respectfully disagree. Claim 51 as amended recites in part "A³ may be substituted with a group selected from X²R⁹." Thus, the claims are not indefinite.

The Examiner is of the opinion that claims 57-59 are indefinite as "it is not known what is meant by the definition of A¹ is -R³. It is believed that the applicants' intended X²R³."

Applicants respectfully disagree. Claim 57 as amended recites in part "A¹ may be substituted with a group selected from X²R³." Thus, the claims are not indefinite.

The Examiner is of the opinion that claims 57-61 are indefinite as "it is not known what is meant by the definition of A² is -R⁸. It is believed that the applicants' intended X²R⁸."

Applicants respectfully disagree. Claim 57 as amended recites in part "A² may be substituted with a group selected from X²R⁸." Thus, the claims are not indefinite.

The Examiner is of the opinion that claims 57-61 are indefinite as "it is not known what is meant by the definition of A³ is -R⁹. It is believed that the applicants' intended X²R⁹."

Applicants respectfully disagree. Claims 57 and 61 as amended recite in part "A³ may be substituted with a group selected from X²R⁹." Thus, the claims are not indefinite.

The Examiner is of the opinion that claim 62 is indefinite as there is insufficient antecedent basis for the limitation "benzo[b][1,4]thiazepin-4-yl" in three of the species.

Applicants respectfully disagree. Claim 62 as amended does not recite the limitation "benzo[b][1,4]thiazepin-4-yl." Thus, the claim is not indefinite.

The Examiner is of the opinion that claim 64 is indefinite as there is insufficient antecedent basis for the limitation "benzo[b][1,4]thiazepin-4-yl" in two of the species.

Applicants respectfully disagree. Claim 64 as amended does not recite the limitation "benzo[b][1,4]thiazepin-4-yl." Thus, the claim is not indefinite.

The Examiner is of the opinion that claims 66-68 are indefinite as "it is not known what is meant by the definition of A¹ is -R³. It is believed that the applicants' intended X²R³."

Applicants respectfully disagree. Claim 66 as amended recites in part "A¹ may be substituted with a group selected from X²R³." Thus, the claims are not indefinite.

The Examiner is of the opinion that claim 66-70 are indefinite as "it is not known what is meant by the definition of A² is -R⁸. It is believed that the applicants' intended X²R⁸."

Applicants respectfully disagree. Claim 66 as amended recites in part "A² may be substituted with a group selected from X²R⁸." Thus, the claims are not indefinite.

The Examiner is of the opinion that claims 66-70 are indefinite as "it is not known what is meant by the definition of A³ is -R⁹. It is believed that the applicants' intended X²R⁹."

Applicants respectfully disagree. Claims 66 and 70 as amended recite in part "A³ may be substituted with a group selected from X²R⁹." Thus, the claims are not indefinite.

The Examiner is of the opinion that claim 71 is indefinite as there is insufficient antecedent basis for the limitation "benzo[b][1,4]thiazepin-4-yl" in three of the species.

Applicants respectfully disagree. Claim 71 as amended does not recite the limitation "benzo[b][1,4]thiazepin-4-yl." Thus, the claim is not indefinite.

The Examiner is of the opinion that claims 76-78 are indefinite as "it is not known what is meant by the definition of A¹ is -R³. It is believed that the applicants' intended X²R³."

Applicants respectfully disagree. Claim 76 as amended recites in part "A¹ may be substituted with a group selected from X²R³." Thus, the claims are not indefinite.

The Examiner is of the opinion that claims 76-78 are indefinite as "it is not known what is meant by the definition of A² is -R⁸. It is believed that the applicants' intended X²R⁸."

Applicants respectfully disagree. Claim 76 as amended recites in part "A² may be substituted with a group selected from X²R⁸." Thus, the claims are not indefinite.

The Examiner is of the opinion that claims 76-80 are indefinite as "it is not known what is meant by the definition of A³ is -R⁹. It is believed that the applicants' intended X²R⁹."

Applicants respectfully disagree. Claims 76 and 80 as amended recite in part "A³ may be substituted with a group selected from X²R⁹." Thus, the claims are not indefinite.

The Examiner is of the opinion that claim 81 is indefinite as there is insufficient antecedent basis for the limitation "benzo[b][1,4]thiazepin-4-yl" in three of the species.

Applicants respectfully disagree. Claim 71 as amended does not recite the limitation "benzo[b][1,4]thiazepin-4-yl." Thus, the claim is not indefinite.

The Examiner is of the opinion that claim 83 is indefinite as there is insufficient antecedent basis for the limitation "benzo[b][1,4]thiazepin-4-yl" in one of the species.

Applicants respectfully disagree. Claim 83 as amended does not recite the limitation "benzo[b][1,4]thiazepin-4-yl." Thus, the claim is not indefinite.

Applicants respectfully submit that all of the stated grounds for the rejection of claims 1-5, 8, 22, 24, 26, 35, 48, 49, 51-64, 66-72, 75-83, and 85-97 under 35 U.S.C. § 112, second paragraph, have been traversed, accommodated or rendered moot. Therefore, Applicants respectfully submit that this rejection should be withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Robert A. Schwartzman, Ph.D.
Agent for Applicants
Registration No. 50,211

Date: July 23, 2003

1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600

::ODMA\MHODMA\SKGF_DC1;149791;1

SKGF Rev. 4/22/03 mac; 6/12/03 svb